Testicular cancer: current update and controversies

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Testicular cancer is an important disease affecting young men. The overall 5-year survival has improved to 95%. The goal now is to maintain the efficacy of treatment in advanced disease while reducing the associated side effects.

Testicular cancer is relatively uncommon. However, it primarily affects young men and the treatment of radical orchidectomy has a tremendous psychological burden on the patient. The use of serum markers to detect and monitor treatment, plus the use of platinum-based agents for metastatic disease, have resulted in an overall 1- and 5-year survival rate of almost 98% and 95% respectively (Quinn et al, 2001). The quest is for therapeutic modalities for metastatic disease that have superior efficacy but better side-effect profiles so that the quality of life, e.g. sexual function and fertility, can be preserved.

EPIDEMIOLOGY

Although testicular cancer only accounts for about 1% of all malignancies in men at all ages, it is the commonest cancer in men between 20 and 34 years of age (Quinn et al, 2001). Approximately 50% of all testicular cancers occur in men under 35 years of age. The incidence in the UK in 1996 was 1770 while there were 90 deaths from testicular cancer in 1998 (Quinn et al, 2001). The incidence has nearly doubled since 1971. This may be caused by endogenous or exogenous (environmental) oestrogenic compounds that affect the embryonic testis and increase the subsequent risk of carcinogenesis (Sharpe and Skakkebaek, 1993).

RISK FACTORS

There are a number of suggested risk factors for testicular cancer (*Table 1*). The role of testicular microlithiasis (TM) as a risk factor has been widely debated. TM is an ultrasound (US) appearance of 'innumerable tiny bright echoes diffusely and uniformly scattered throughout the substance of the testicle' (Doherty et al, 1987). It occurs in more than 5% of healthy young men (Peterson et al, 2001). The same group concluded that TM is a common finding in asymptomatic men and may not be related to testicular cancer. However, opposing evidence exists where interval testicular cancer was found in 5.4% of patients during follow-up US (Otite et al, 2001). Since germ cell tumours develop from carcinoma in situ (CIS), it would be useful to diagnose testicular cancer at this early stage. Although CIS is asymptomatic, it is associated with the presence of TM. Therefore, some advocate testicular biopsy when TM is found (Holm et al, 2001).

Trauma and vasectomy have not been proven as risk factors. However, non-manual or professional workers have a higher incidence of testicular cancer (Quinn et al, 2001).

PATHOLOGY

The histopathology of testicular tumours is complex. A simplified classification is shown in *Table 2*, using the British sub-classification of non-seminomatous germ cell tumours (NSGCT; Pugh and Cameron, 1976).

TABLE 1.
Suggested risk factors for developing testicular cancer

Factor	Relative risk
Testicular maldescent	≥3.8 if orchidectomy not performed
Infantile hernia	1.9
Low birth weight	2.6
Positive family history, e.g. siblings of patients	6–10, found to be associated with Xq27 mutation (Rapley et al, 2000)
Geographical/environmental/ lifestyle/genetic factors	E.g. American Blacks have roughly 3 times less risk than American Whites but 10 times more risk than African Blacks
In-utero exposure to oestrogen	5
Carcinoma in situ	50% of patients will develop testicular cancer within 5 years
History of contralateral testicular cancer	28
Testicular microlithiasis	Not clearly defined at present but biopsy advocated by some (see text)

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TABLE 2.
Histological classification of testicular cancer

Anatomical origin			Histological type		
Primary tumour (~50%)	Germinal elements (~90–95%)	Germ cell tumours	Seminoma		
			NSGCT (~33%)	Teratoma differentiated	
				Malignant teratoma	Intermediate
					Undifferentiated
					Trophoblastic
				Yolk sac tumour	
			Mixed tumours (~10%)		
	Non-germinal elements (~5%)	Non-germ cell tumours	Specialized gonadal stromal neoplasms	Leydig cell tumour	
				Other gonadal stromal tumours	
				Gonadoblastoma	
				Miscellaneous tumours, e.g. carcinoid	
Secondary tumour		Reticuloendothelial tumours		e.g. lymphoma	
		Metastases			

NSGCT = Non-seminomatous germ cell tumours

TABLE 3.
The Royal Marsden Hospital staging system for testicular cancer

Stage	Description		
I	No evidence of metastasis	IM	Rising concentrations of serum markers without other evidence of metastasis
II	Abdominal lymphadenopathy	A	≤2 cm in diameter
		B	2–5 cm in diameter
		C	≥5 cm in diameter
III	Supra-diaphragmatic lymphadenopathy	M	Mediastinal
		N	Supraclavicular, cervical or axillary
		0	No abdominal lymphadenopathy
		A, B or C	Nodal status as defined in Stage II
IV	Extra-lymphatic metastasis	Lung	L1 ≤3 metastases
			L2 ≥3 metastases, all ≤2 cm in diameter
			L3 ≥3 metastases, one or more of which are ≥2 cm in diameter
		Liver	H+ Liver metastases
			Br+ Brain metastases
			Bo+ Bone metastases

From Horwich (1995)

TABLE 4.
Prognostic groups for non-seminomatous germ cell tumours

Prognostic group (proportion of patients)	AFP (μg/ml)	hCG (IU/ml)	LDH (x normal)	Presence of non-pulmonary metastases	5-year survival rate (%)
Good (56%)	<1	<5	<1.5	No	92%
Intermediate (28%)	1–10	5–50	1.5–10	No	80%
Poor (16%)	>10	>50	>10	Yes	48%

From International Germ Cell Cancer Collaborative Group (1997). AFP=alpha-fetoprotein, hCG=human chorionic gonadotrophin, LDH=lactic acid dehydrogenase

Testicular tumours metastasize via the lymphatic (initially to the para-aortic nodes), and haematogenous routes (commoner in NSGCT, to the lungs, liver and brain).

STAGING

Staging allows important management decisions to be made and provides prognostic information. With the introduction of alternative treatment protocols for low-stage disease, its accuracy and impact become even more crucial. There are many systems in use and an example is shown in *Table 3*.

PROGNOSTIC FACTORS

Apart from staging, the International Germ Cell Cancer Collaborative Group (IGCCCG, 1997) had introduced further criteria incorporating serum markers (pre-treatment levels of alpha-fetoprotein (AFP), human chorionic gonadotrophin (hCG) and lactate dehydrogenase (LDH)) and anatomical features (the primary tumour site and the presence of non-pulmonary visceral metastases). These parameters were found to be the most important independent prognostic factors for survival in NSGCT (*Table 4*). A similar table (*Table 5*) is shown for seminoma.

DIAGNOSIS

Diagnosis is based on history, physical examination and investigations, including histological examination after radical orchidectomy (*Figure 1*).

History

The presenting features are summarized in *Table 6*.

Examination

It is important to differentiate lumps arising from the testis from other intra-scrotal structures, e.g. epididymis, or inguinal scrotal swellings. Patients with epididymo-orchitis or orchitis who have not improved within 2 weeks should be referred for an urgent urological opinion according to the Clinical Oncology Information Network (2000).

Investigations

Imaging: US is non-invasive and can confirm a testicular lesion in most cases. Computed tomography (CT) plays an important role in the staging and follow up of patients. Positron emission tomography may have an important role in detecting residual masses after treatment of advanced disease.

Serum tumour markers: Serum tumour markers (*Table 7*) are important in the diagnosis,

prognosis, monitoring of treatment and follow up of testicular cancer. AFP is a fetal serum-binding protein. It is normally found in minimal quantities (<100 ng/litre) after the first year of life. Pure seminoma does not cause an elevation in AFP. hCG is normally produced by syncytiotrophoblasts of the placenta. Normal men have serum levels of the beta subunit of <5 mIU/ml. LDH is an enzyme responsible for lactic acid oxidation in muscle, liver and kidneys. It is useful as a marker of large volume disease and may be the only biochemical abnormality in as many as 10% of persistent or recurrent NSGCT. Reverse transcription polymerase chain reaction has enabled the differentiation of placental alkaline phosphatase from germ cell-specific alkaline phosphatase. They are elevated in NSGCT and seminoma respectively (Kommoss et al, 2000). Inhibin-alpha is a promising marker for Leydig cell tumours because it is absent from germ cell tumours.

Unfortunately, these markers are not specific for testicular cancer and their use should be correlated with other clinical findings.

TABLE 6.
Presenting features of testicular tumour

	Symptom
Local effects	Painless lump
	Testicular ache/discomfort
	Enlargement or firmness of testis
	Asymmetry
Metastatic effects	Back pain (para-aortic lymphadenopathy)
	Breathlessness or haemoptysis (pulmonary metastasis)

TABLE 7.
Serum tumour markers commonly in use

Tumour marker	Elevated in
AFP	NSGCT (50–60%)
hCG	Choriocarcinoma (100%)
	Embryonal tumour (80%)
	Pure seminoma (10–25%)
LDH isoenzyme 1	Advanced or large volume
	Advanced pure seminoma
PLAP	NSGCT
GCAP	Seminoma
Inhibin-alpha	Leydig cell tumour

AFP=alpha-fetoprotein, GCAP=germ cell-specific alkaline phosphatase, hCG=human chorionic gonadotrophin, LDH=lactic acid dehydrogenase, NSGCT=non-seminomatous germ cell tumour, PLAP=placental alkaline phosphatase

TABLE 5.
Prognostic groups for seminoma

Prognostic group (percentage of patients)	Presence of non-pulmonary metastasis	5-year survival rate (%)
Good (90%)	No	86%
Intermediate (10%)	Yes	72%

NB. No patients were classified as having a poor prognosis. From International Germ Cell Cancer Collaborative Group (1997)

MANAGEMENT

Radical orchidectomy is the conventional initial treatment of testicular cancer. This is done via an inguinal approach without breaching the scrotal skin. In patients with synchronous bilateral testicular cancer or a single testicle, an alternative of organ-sparing surgery may be considered. The feasibility of this option was shown in selected patients with organ-confined tumours of <20 mm and a normal testosterone level (Heidenreich et al, 2001).

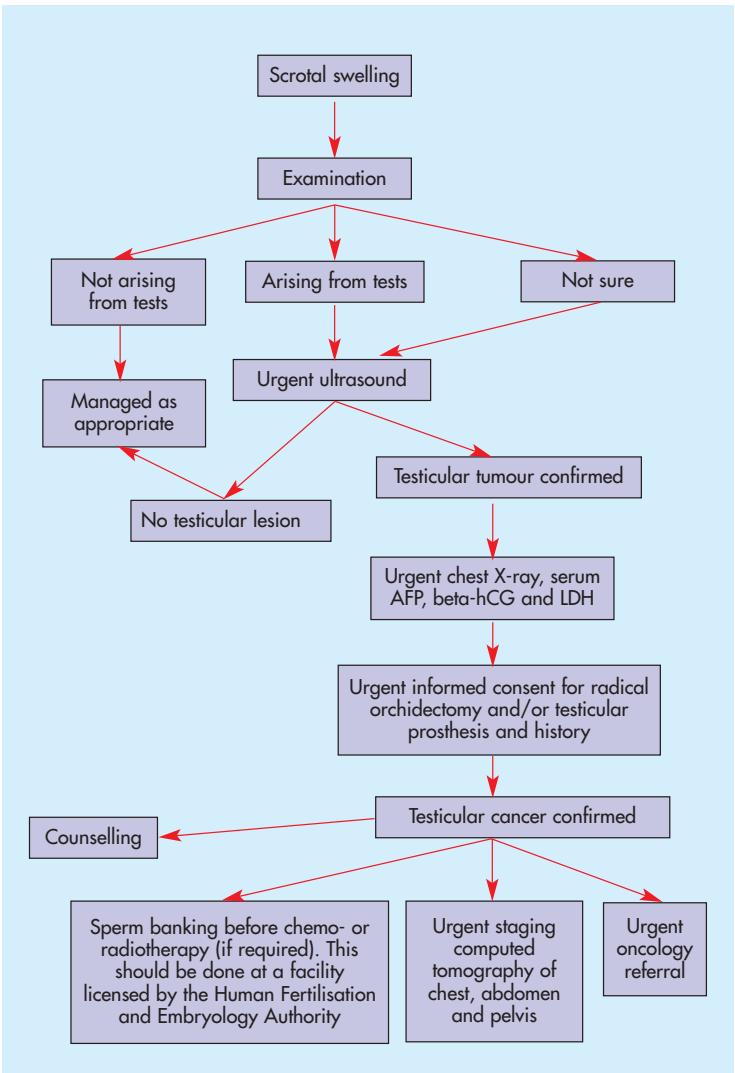

Figure 1. Management of suspected testicular tumour. AFP=alpha-fetoprotein, hCG=human chorionic gonadotrophin, LDH=lactic acid dehydrogenase.

Seminoma

Although 80% of patients are cured by radical orchidectomy alone, surveillance for stage I disease is viewed by some as an investigational approach (Dearnaley et al, 2001) (*Figure 1*). This is because the conventional approach has a high success rate. Furthermore, the serum tumour markers are less reliable in detecting recurrence than in NSGCT, making follow up more difficult. In addition, recurrence may occur years after orchidectomy, but some believe that this practice is safe (Francis et al, 2000; Oliver, 2001).

One difficult problem after chemotherapy for advanced seminoma is the lack of complete resolution of radiographical masses. Surgical resection of such masses is difficult because seminoma involves the retroperitoneum in a fibrotic process similar to retroperitoneal fibrosis. Clean dissection is rarely possible, but if the residual mass was 3 cm or greater, viable tumour was found in about 50% of patients (Motzer et al, 1987). Hence surgical resection is advisable in this group.

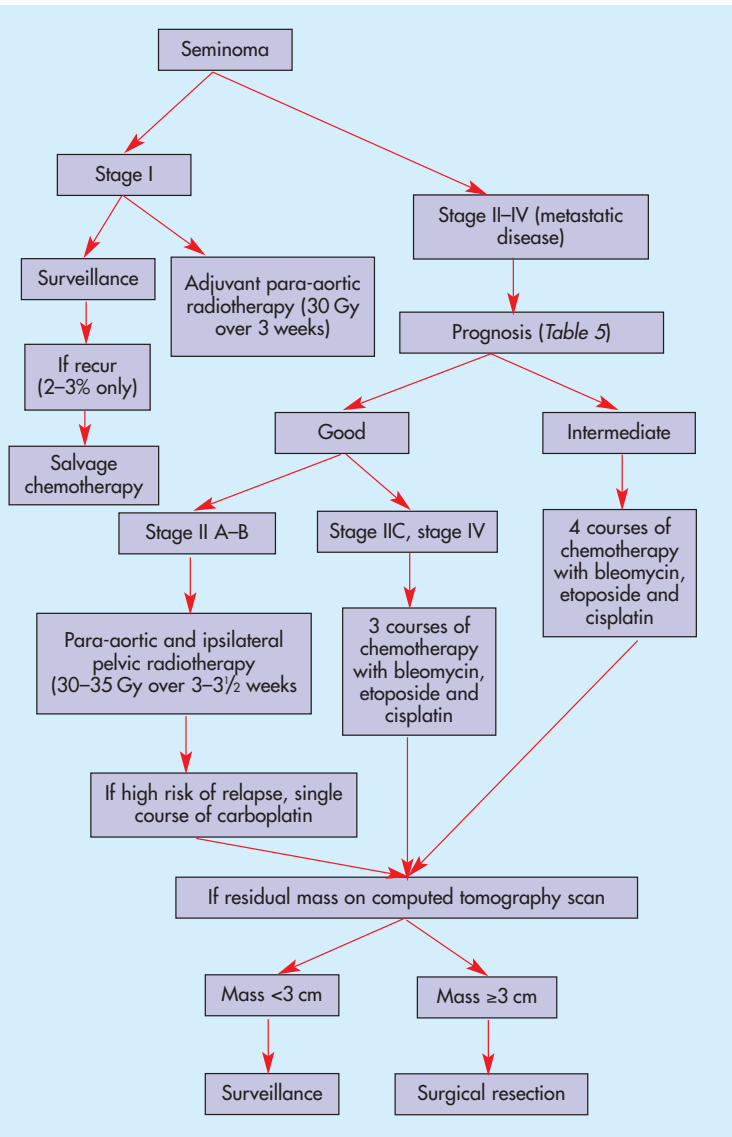

Figure 2. Suggested management of seminoma after radical orchidectomy and staging. The actual regimen may vary according to local expertise, opinion and protocol.

NSGCT

Based on clinical trial results, a strict surveillance protocol was established for the low-risk group in stage I disease, with chemotherapy reserved for the 30% of patients when metastasis developed (Read et al, 1992) (*Figure 2*). The frequency of surveillance CT is currently under review. Alternatively, adjuvant chemotherapy (two courses) could be administered immediately in the high-risk group (Cullen, 1996). With either approach, the overall survival is nearly 100%.

About one third of patients with stage II–IV disease will have residual para-aortic masses after chemotherapy. About 10% of these masses will have active undifferentiated malignant tumours. The remaining masses will contain differentiated teratoma or necrotic and fibrotic tissue. The former is unstable and is probably responsible for the late relapses. Resection of all of these masses is therefore recommended.

Persistent disease

About 15% of patients will not be cured despite a combination of therapy and surgery. They pose a challenging management problem. A combination of high-dose chemotherapy with stem cell support, surgical resection, and occasionally radiotherapy can be used. This will achieve a cure in about 30% of men (Horwich, 1995).

SIDE EFFECTS OF TREATMENT

Chemotherapy

These side effects are summarized in *Table 8*.

Surgery

Retroperitoneal lymph node dissection can cause infertility as a result of either failure of seminal emission or retrograde ejaculation secondary to damage to the sympathetic fibres involved in ejaculation. Modification and improvement in surgical technique allowed return of ejaculation in approximately 50–90% of the patients after surgery, depending on the side and the stage of the tumour.

FOLLOW UP

This is an integral part of the management of patients with testicular cancer. Apart from monitoring the effect of treatment, detecting contralateral cancer, treatment-related toxicity and relapse at an early stage when salvage treatment

is still effective, it provides support and counselling to patients and their partners.

While a regimen had been described in the Clinical Oncology Information Network of the Royal College of Radiologists (2002), the optimum timing for clinical and radiological follow up is still controversial. It has been suggested that all patients with seminoma and those with stage I NSGCT may be discharged 5 years after treatment (Dearnaley et al, 2001). However, metastatic NSGCT continue to have an annual relapse rate of 1–2%, even after 10 years. The same group suggested that longer term follow up is necessary (Dearnaley, 2001).

Follow up by a specialist centre has the advantages of a multidisciplinary team approach, access to databases of large numbers of patients, and the possibility of auditing results. However, this may not be convenient for all patients and follow up by GPs with an interest in this area and easy access to the specialist centre may be an alternative.

TABLE 8.
Side effects of chemotherapy

Short term	Nausea and vomiting	
	Fatigue	
	Alopecia	
	Neutropenia and sepsis	
	Nephropathy	
Long term	From bleomycin	Pulmonary toxicity
		Changes in skin pigmentation and nails
		Raynaud's syndrome
	From cisplatin	Peripheral and auditory nerve neuropathy
		Avascular necrosis of the hip
	Azoospermia (irreversible in 20–30% of patients)	
	Second malignancy e.g. leukaemia. This risk applies to both chemotherapy and radiotherapy (Travis et al, 2000)	
	Increase in cardiac events (Meinardi et al, 2000)	

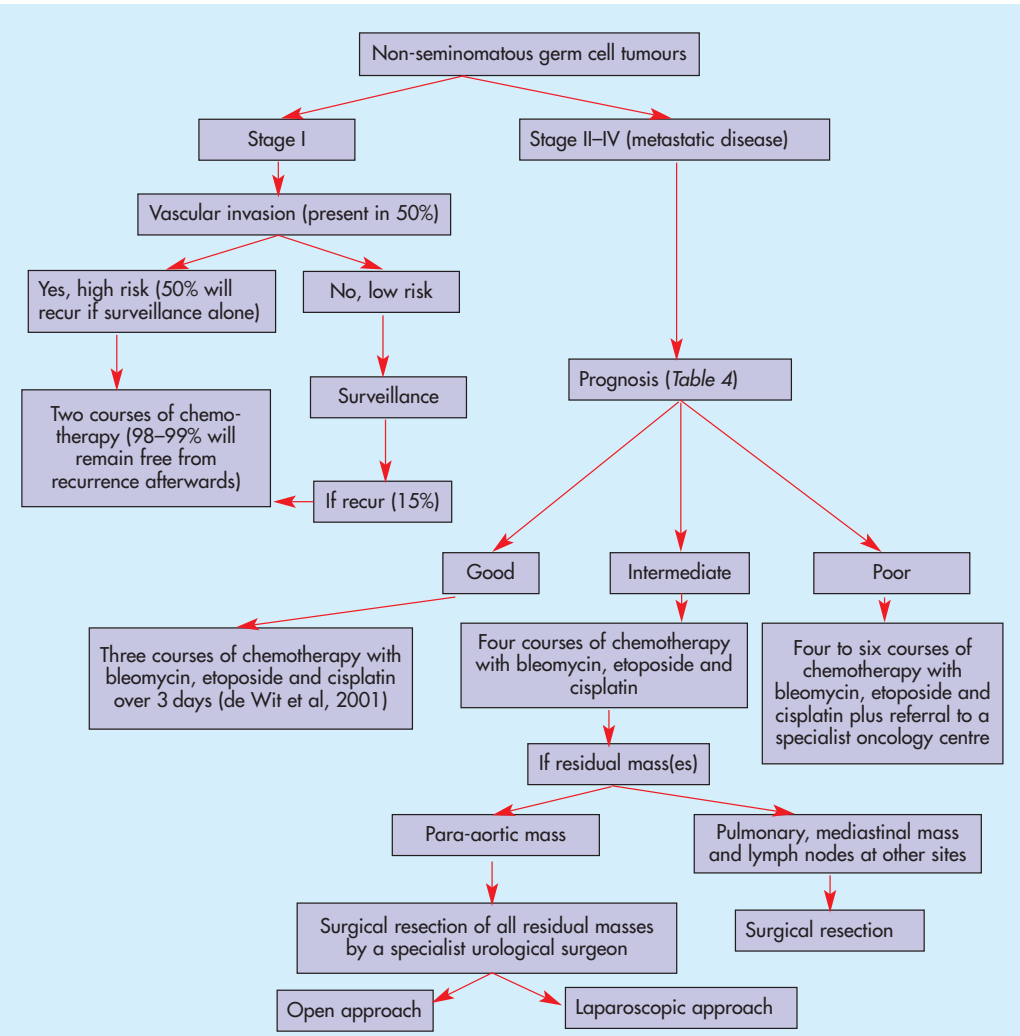

Figure 3. Suggested management for non-seminomatous germ cell tumours after radical orchidectomy and staging. The actual regimen may vary according to local expertise, opinion and protocol.

ON THE HORIZON

Experimental prognostic factors

These are summarized in *Table 9*. More research is required to prove their value as prognostic factors.

Clinical trials

For seminoma, trials are being conducted to assess whether the dose of radiation can be reduced to 20 Gy for stage I disease and to assess the use of carboplatin as a single agent. For NSGCT, studies are underway to investigate new agents like paclitaxel, 'dose intense' schedules using weekly treatment and high dose treatment with stem cell rescue for patients with a poor prognosis. Efforts are being made in search of less toxic platinum-based regimen, and the use of vanadium-containing agents is being studied (Ghosh et al, 2000).

CONCLUSIONS

Although the overall survival rate for testicular cancer is very good, there is still room for improvement in the treatment of advanced disease, maintaining the high cure rate while reducing the associated morbidity and toxicity. HM

Conflict of interest: none.

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TABLE 9.
Experimental prognostic factors

Marker	
Cell proliferation markers (Moul et al, 1993)	DNA index
	S-phase fraction
	Proliferation index
Molecular markers (Bosl et al, 1989)	Isochromosome 12p
Protooncogene (Strohmeyer et al, 1991)	hst-1

KEY POINTS

- Testicular cancer is the commonest cancer in men aged 20–34 years of age.
- Men should be made aware of testicular cancer and its presenting symptoms, especially if there is a history of maldescended testis or family history of testicular cancer.
- Advanced and recurrent disease should be managed by a multidisciplinary team.
- Microlithiasis may be associated with testicular cancer and may be a precursor lesion.
- Routine testicular self-examination is helpful.